REMARKS

The foregoing amendments in the specification are of formal nature, and do not add new matter. Claims 39-44 are pending in this application and stand rejected on various grounds.

Objections

The disclosure was objected to by the Examiner as containing "embedded hyperlink / and/or other form of browser-executable code." The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections.

Priority

The Examiner has concluded that applicants are entitled only to the filing date of the present application which is July 11, 2001. As it will be apparent from the rest of the response, Applicants rely on the gene amplification assay results (Example 92) to establish substantial and specific asserted utility for the polypeptide PRO343. These results were first disclosed in international application PCT/US99/30095 (P2509R1), filed December 16, 1999 and published as WO 00/37640 on June 29, 2000 and which claims priority to US provisional Application No. 60/113,296 (P2509), filed December 22, 1998. Support is present at least at pages 133-137, pages 154-155 and pages 116-121of the WO 00/37640 publication. Accordingly, the present application is entitled to the filing date of December 22, 1998.

Claim Rejections under 35 U.S.C. 101

Claims 39-44 were rejected under 35 U.S.C. 101 "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." The Examiner specifically noted that "the specification provides no working examples as to the activity of the PRO343 polypeptide, and one of ordinary skill in the art would not be able to predict what activity of the PRO343 polypeptide, and one of ordinary skill in the art would not be able to predict what activity would be possessed by the protein of the instant application, based solely it might be expressed in some primary lung or colon tumor or cell lines."

The rejection is respectfully traversed.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Proper Application of the Legal Standard

Applicants submit that the gene amplification data provided in the present application are sufficient to establish a specific, substantial and credible utility for the PRO343 polypeptide.

Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 92 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 230-234 of the specification), including primary lung cancers of the type and stage indicated in Table 8 (page 227). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 222, lines 34-36). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. As explained in the passage bridging pages 222 and 223, the results of TaqMan™ PCR are reported in ΔCt units. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification. PRO343 showed approximately 2-3-fold amplification in 6 primary lung tumors, approximately 4-fold amplification in 3 primary lung tumors, approximately 8-fold amplification in 2 primary lung tumors, approximately 2-3 fold amplification in 13 primary colon tumors and approximately 4-9 fold in 5 primary colon tumors.

In assessing the value of these data, the Examiner notes that: "There is no specific information on what type of the normal tissue was used as a control and how many normals there were. A single normal sample is not sufficient for basing relative levels of many other samples." The Examiner has apparently overlooked that, as discussed above, control DNA was pooled from the cells of ten normal healthy individuals (page 222, lines 34-36). Accordingly, the results are not based on a single normal sample. The samples were obtained from blood. cells as it is usual in similar gene amplification assays.

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan™ real-time PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The Declaration also confirms that based upon the gene amplification results set forth in Table 9 one of ordinary skill would find it credible that PRO343 is a diagnostic marker of human lung and colon cancer. It is, of course, true that further research would be needed to develop PRO343 into

a diagnostic product. Such follow-up tests could include the mapping of the PRO343 gene to a chromosome, which could be followed, for example, by dual-color FISH with DNA probes complementary to the PRO343 gene and the centromere of the chromosome to distinguish a locus-specific gene amplification from chromosome aneuploidity. However, the fact that such follow-up tests might be necessary, cannot properly lead to the legal conclusion that PRO343 lacks patentable utility.

As set forth in M.P.E.P, 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The attached Declaration by Audrey Goddard establishes that the asserted utility in viewed "credible" by one skilled in the art. Indeed, the logic underlying Applicants' assertion that PRO343 is a diagnostic marker of lung and colon cancer cannot be viewed as "seriously flawed," and the facts upon which the assertion is based are not inconsistent with the logic underlying the assertion. It is always possible that an invention fails on its way of development to a commercial product. Thus, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections under 35 U.S.C. 112, first paragraph

Claims 39-44 were rejected under 35 U.S.C. 112, first paragraph because "one skilled in the art clearly would not know how to use the claimed invention." The Examiner noted that "although the specification describes the structure of PRO343 polypeptide, and one of ordinary skill in the art can make antibodies against it, the skilled artisan would not know how to use said PRO343 polypeptide or antibodies against it, the skilled artisan would not know how to use said PRO343 polypeptide or antibodies against it, because Applicants do not provide any information regarding biological activity or physiological characterization of said polypeptide."

In response to the previous rejection under 35 U.S.C. 101, Applicants have shown that undue experimentation is not required of the skilled artisan to use the claimed invention and that

the specification discloses a substantial, specific and credible utility for the PRO343 polypeptide or antibodies against it. This specific utility is now recited in the rejected claims, which is believed to overcome the present rejection. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of all pending claims under this section.

Claim Rejections under 35 U.S.C. 102(b)

Claims 39-40, 42-44 were rejected under 35 U.S.C. 102(b) "as being anticipated by Amrad Operations Pty. Ltd (WO 98/36054; published 20 August 1998)." According to the rejection, "Amrad Operations Pty. Ltd discloses an isolated polypeptide that shares 86.3% over all homology and 100% homology from amino acid residue 47 to amino acid residue 317 of the polypeptide of SEQ ID NO: 263 of the instant application," and "also discloses an antibody, (monoclonal, polyclonal, fragment of antibody or which may be associated with a carrier molecule)."

Applicants respectfully disagree. SEQ ID NO: 263 of the instant application represents a polypeptide of 317 amino acids while the polypeptide of Amrad Operations Pty. Ltd is 217 amino acids in length. Alignment of the two sequences as taught in the present application (see attachment) results in 271 matches out of 317 amino acids, which corresponds to 85.48% overall identity.

The claims as currently amended concern an antibody that binds specifically to the polypeptide of SEQ ID NO: 263. As such antibodies, by definition, do not bind to a polypeptide that has about 85% overall sequence identity with SEQ ID NO: 263, they are not anticipated by Amrad Operations Pty. Ltd. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections under 35 U.S.C. 103

Claims 39 and 41 were rejected under 35 U.S.C. 103(a) "as being unpatentable over Amrad Operations Pty. Ltd. (WO 98/36054) in view of Carter et al. (U.S. Patent 5,821,337). Amrad Operations Pty Ltd. was applied as in the previous rejection. Carter et al. was cited for its disclosure of humanized antibodies. As shown in response to the previous rejection, Amrad et al. does not anticipate the rejected claims. Accordingly, its combination with Carter et al., which is applied only to show that humanized antibodies were known in the art at the effective

date of the present application, does not make obvious the claims pending. Applicants respectfully request the reconsideration and withdrawal of the present rejection.

Attached hereto is a marked-up copy of the amendments made in the specification and claims. The attached sheets are entitled "**Version with Markings to Show Changes Made**:"

All claims are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for extension of time, or credit overpayment to Deposit Account No. . 08-1641

Respectfully submitted,

HELLER EHRMAN WHITE & McAULIFFE LLP

Dated: February 7, 2003

By: _____
Ginger R. Dreger
Registration No. 33,055
Attorney of Record

Version with markings to show changes made

In the Specification:

The paragraph, beginning at page 69, line 6, has been amended as follows:

--Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph, beginning at page 71, line 26, has been amended as follows:

--Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph beginning at page 147, line 27, has been amended as follows:

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul, and Gish, Methods in Enzymology 266: 460-80 (1996)[; http://blast.wustl/edu/blast/README.html]) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a Blast score of 70 (or in some cases 90) or greater that did not encode known

proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

The paragraph, beginning at page 154, line 14, with the following rewritten paragraph:

--The EST sequence accession number AF007268, a murine fibroblast growth factor (FGF-15) was used to search various public EST databases (e.g., GenBank, Dayhoff, etc.) The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)[; http://blast.wustl/edu/blast/README.html]] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. The search resulted in a hit with GenBank EST AA220994, which has been identified as stratagene NT2 neuronal precursor 937230.--

The paragraph beginning at page 167, line 30, was amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; http://bozeman.mbt.washington.edu/phrap.docs/phrap.html]).

The paragraph beginning at page 178, line 14, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program

BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; http://bozeman.mbt.washington.edu/phrap.docs/phrap.html]).--

In the Claims:

Claim 44 has been canceled.

Claim 39 has been amended as follows:

39. (Once amended) An antibody that specifically binds to the polypeptide shown in Figure 98 (SEQ ID NO: 263).

AMEND
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